PATENT

6193/1

UNITED STATES PATENT APPLICATION

for

COMPOSITION AND METHOD FOR RECTAL DELIVERY OF A LINCOSAMIDE ANTIBACTERIAL DRUG

by

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COMPOSITION AND METHOD FOR RECTAL DELIVERY OF A LINCOSAMIDE ANTIBIOTIC DRUG

CROSS REFERENCE TO RELATED APPLICATIONS

The present patent application is a continuation-in-part of U.S. Patent Application Serial No. 09/619,930, filed July 20, 2000, that claims the benefit of U.S. Provisional Patent Application Serial No: 60/147561, filed August 6, 1999.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition useful for rectal application for treatment or prevention of infective disease. In particular, the present invention relates to a rectal formulation of a lincosamide antibacterial drug that can be used for treatment or prevention of infection by a gram-positive bacterial agent. The field of the present invention also includes therapeutic or prophylactic use of such a formulation, and use of such a formulation in preparation of a medicament.

BACKGROUND OF THE INVENTION

Lincosamide compounds have been reported having therapeutically and/or prophylactically useful antibiotic, in particular antibacterial, effect. Lincosamides, such as clindamycin, lincomycin, and pirlimycin, have long been recognized as antibiotics active against bacteria, primarily, against gram-positive bacteria. Lincosamides are known to prevent translocation of nascent polypeptide, making the class of compounds useful for the treatment of a variety of disorders related to bacterial infections.

Clindamycin has long been recognized as being particularly effective in the treatment of staphylococcal infections. Several commercial formulations of clindamycin designed for oral administration can be found on the market, including CLEOCIN® HCL (Pharmacia Corporation, NJ, USA), an oral formulations of clindamycin hydrochloride designed for adults, and CLEOCIN® PEDIATRIC (Pharmacia Corp.), an oral formulation of clindamycin palmitate hydrochloride designed for children. In such formulations clindamycin hydrochloride and

clindamycin palmitate hydrochloride are hydrolyzed to clindamycin free base in the gastrointestinal tract of a subject, prior to being absorbed into the bloodstream.

U.S. Pat. No. 4,289,757 discloses various methods of treating inflammation in mammals suffering from "an inflammatory condition not associated with a microbial component." ('757 Patent, Abstract). The methods of treatment include topical application of an antibiotic, such as clindamycin or lincomycin, according to a variety of different means, including administration through rectal or vaginal suppositories. ('757 Patent, col. 3, line 35). However, no guidance is provided therein as to a suitable composition for any such suppository.

It is well known that, although parenteral and oral routes of administration may be excellent for systemic delivery of drugs to many subjects, these routes may be less suitable for particular classes of subjects. For example, some human subjects such as small children, small adults, and elderly individuals have problems in swallowing a medication, or are otherwise incompliant with attempts at oral administration. Non-human subjects may also refuse to comply with attempts at oral administration of drugs. Parenteral administration, such as through injection, also has disadvantages, for example in a requirement for administration by trained personnel and in a fear or sensation of pain that can be associated with such administration.

Formulations, such as vaginal suppositories or topical creams, that permit one to administer a drug to a subject through the vagina offers several advantages over oral and parenteral means, described above. See, for example, vaginal suppositories of clindamycin disclosed in International Application No. PCT/US00/19533, published as WO 01/10407, incorporated by reference herein. The present application claims priority to the same U.S. provisional application cited therein, through a U.S. counterpart of the International Application, U.S. Patent Application No. 09/619,930. WO 01/10407 does not disclose the administration of any licosamides other than clindamycin, nor does it suggest that any such composition be rectally administered. Depending upon the composition of the formulation, such formulations enable one to treat bacterial infections in the vagina of a subject alone, and/or to introduce the active agent into the blood stream and into various other parts and systems of the subject. Naturally, vaginal administration is only available to a certain portion of the population of any given subject species.

The rectal route of administration offers several advantages over other means of administration, including the availability of the means of delivery to all members of a species, regardless of gender, throat size, or aversion to needles. Various types of suppositories have been described as being useful for rectal delivery of any one of a number of different active agents into a subject, including lincosamides, such as clindamycin or lincomycin. See, for example, U.S. Patent No. 4,289,757 by E. Myles Glen; EO 0 206 947 by Jose Alexander; WO 99/29299 by Rudolf Linder; and U.S. Patent No. 4,464,466 by Alexander Argoudelis.

To the extent that the active agent is described in any such references, it is disclosed as being present in a suppository in the form of a liquid. However, vaginal suppositories have been developed wherein the active agent is present within porous particles, such as microsponges, contained within each suppository. See, for example, WO 97/44032. Such formulations inherently limit the amount of active agent one can fit into a suppository, as a solution of active agent can only be concentrated so far before it reaches its saturation point. In some cases, a single dose of a given active agent cannot fit into a single suppository. Left in liquid form, many active agents, including lincosamides, tend to degrade over time within a suppository composition.

What is needed is a stable rectal suppository formulation of a lincosamide that enables one to effectively deliver an appropriate dose to any given subject. The development of suppository formulations that enable one to do so requires that a number of different factors be taken into consideration, some of which factors are completely unpredictable. A combination of active agent, carrier, and/or other components must be selected to produce a suppository that is solid at room temperature, yet dissolves to release the active agent contained therein after delivery to the rectum of the subject. It is even more difficult to develop such a suppository wherein the active agent is stable. The present invention offers a stable suppository formulation of a lincosamide with such properties.

SUMMARY OF THE INVENTION

In one embodiment, the present invention is a suppository composition for rectal administration of a lincosamide antibacterial drug, the composition comprising an antibmicrobially effective amount of the lincosamide dispersed in a Hard Fat

suppository base, wherein the lincosamide is in the form of solid particles. Suppositories of the present invention can be used to effect systemic delivery of a lincomycin to a subject, by rectal administration.

In another embodiment, the present invention is a method of rectally administering such a suppository composition to a subject.

In yet another embodiment, the present invention is a method of treatment of a subject infected with at least one gram-positive bacteria by rectally administering a series of doses of the suppository composition to the subject until the infection has substantially subsided or disappeared.

It is generally understood that partitioning of an active agent, such as the lincosamide of the present suppository composition, into the rectal membrane is more readily achieved when the active agent is administered in solution than it is when administered in particulate form. Surprisingly, formulations of the present invention, where an active agent is present in particulate form, exhibit high systemic bioavailability of the active agent following rectal administration, even when solubility of the active agent in the carrier is low.

The presence of the active agent in particulate form in the Hard Fat, rather than dissolved in the Hard Fat or in other components of the suppository composition of the present invention, allows for a smaller volume of suppository composition to be administered for a given dose; because, the lincosamide loading is not limited by solubility in the carrier. This makes the administration more practical and convenient to the subject. This is especially important where the maximum tolerable volume of administration is small, as for example where the subject is an infant or neonate.

Due to the fact that the lincosamide antibacterial drug in the present composition is dispersed in particulate form in the carrier, rather than dissolved in the carrier, the chemical stability of the composition of the present invention is typically better than for a composition where the drug is dissolved in the carrier. For example, certain drugs that exhibit chemical instability in solution are less prone to such instability when dispersed in a carrier in which they are poorly soluble or insoluble.

The absorption rate of the lincosamide antibacterial drug can be modified by varying the particle size of the lincosamide in a composition of the invention. This is not an option in a composition where an active agent is dissolved in the carrier.

The composition of the present invention comprises a Hard Fat, a lipophilic type of carrier can be formulated as suppositories that melt at body temperature and consequently are able to release the lincosamide without dissolution of the suppository. This is in contrast to hydrophilic suppositories, which normally are dependent on dissolution to release the lincosamide.

Other features and benefits of the invention will become more apparent from the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows an x-ray diffraction pattern of the different polymorphic transitions that a Hard Fat NF suppository base containing clindamycin will go through over time.

Figure 2 is a schematic of a system for preparing suppositories of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a pharmaceutical composition suitable for rectal administration to treat and/or prevent a bacterial infection, such as a gram-positive bacterial infection. The composition comprises at least one lincosamide antibacterial drug in particulate form, dispersed in a pharmaceutically acceptable carrier in which the lincosamide is poorly soluble. The carrier is preferably lipophilic. The total concentration of lincosamide antibacterial drug in the composition is preferably an antimicrobially effective concentration for rectal administration to and treatment of or prophylaxis of a gram-positive bacterial infection of a subject. The composition preferably further comprises at least one pharmaceutically acceptable excipient.

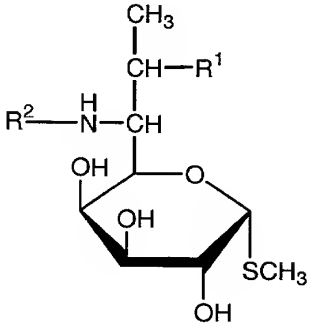
In one embodiment, the composition comprises an antimicrobially effective amount of a lincosamide or a pharmaceutically acceptable salt or ester thereof dispersed in a Hard Fat base. The Hard Fat suppository base used in the compositions of the present invention is preferably a Hard Hat NF grade suppository base. Hard Fat bases, particularly, Hard Fat NF suppository bases, provide an active agent having high stability and efficacy in treating disorders caused by bacteria.

As used herein, the term "Hard Fat base" refers to a mixture of glyceride esters of higher saturated fatty acids. The mixture of triglycerides, diglycerides and monoglycerides making up a Hard Fat may be obtained either by esterification of fatty acids of natural origin with glycerol or by transesterification of natural fats. Each type of Hard Fat is characterised by its melting point, its hydroxyl value and it saponification value.

As used herein, the term "Hard Fat NF base" or "Hard Fat NF suppository base" refers to any Hard Fat base that falls within the National Formulary specifications for such bases.

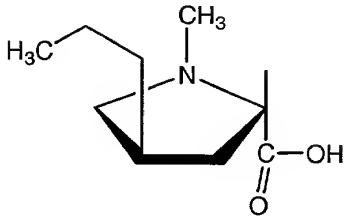
The Hard Fat base used in the composition of the present invention is preferably soft at room temperature. Surprisingly, when a relatively soft Hard Fat base is combined with a lincosamide or a pharmaceutically acceptable salt or ester thereof, the resulting formulation is harder at room temperature than the Hard Fat base alone, yet has a sufficiently low flow point to melt upon rectal administration to a warm-blooded subject.

The term, "lincosamide" is known. It generally refers to a compound that comprises an amino acid linked to an amino sugar, that has bacteriostatic and bactericidal properties, and that inhibits protein synthesis. Lincosamides are believed to inhibit protein biosynthesis by reversibly binding to the 50S ribosomal subunit, preventing polypeptide chain elongation. A preferred lincosamide used in the methods and compositions of the present invention is a compound according to formula (I):



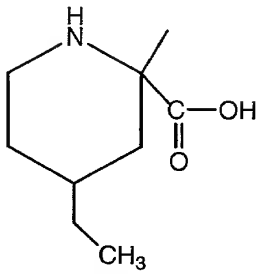
wherein R^1 is H, Cl, Br, or I;

and R^2 is the acyl radical of a carboxylic acid selected from the group consisting of:



(A)

and



(B)

The lincosamide used in the compositions and methods of the present invention preferably includes free-base and crystalline free-base forms, as well as pharmaceutically acceptable salts and esters of the compound of formula (I).

Particularly preferred lincosamides used in the compositions of the present invention include, but are not limited to, clindamycin, lincomycin, and pirlimycin. See discussion of lincosamides in WO 89/04672 by Jean Brison.

One of the lincosamides, clindamycin, is also known as methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-α-D-galacto-octo-pyranoside or methyl 7-chloro-6,7,8-trideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-L-threo-α-D-galacto-octo-pyranoside. As used herein the term "clindamycin" alone includes free-base and crystalline free-base forms of clindamycin as well as the pharmaceutically acceptable salts and esters thereof. Examples of clindamycin pharmaceutically acceptable salts and esters are clindamycin hydrochloride, clindamycin phosphate, clindamycin palmitate and clindamycin palmitate hydrochloride. When clindamycin is used in the composition or method of the present invention, it is preferably in the form of clindamycin crystalline free base or a clindamycin salt or ester, more preferably a clindamycin salt or ester, with clindamycin phosphate being particularly preferred.

The uses, properties and methods of synthesis of clindamycin are set forth in U.S. Patent 3,969,516, Stoughton, issued July 13, 1976; U.S. Patent 3,475,407, Bierkenmeyer, issued in 1969; U.S. Patent 3,487,068, issued in 1969; U.S. Patent

3,509,127 and 3,544,551, Kagan and Magerlein, issued in 1970; U.S. Patent 3,513,155, Bierkenmeyer and Kagan, issued in 1970; Morozowich and Sinkula, U.S. Patent 3,508,904 issued in 1971 and 3,655,885 issued in 1972; U.S. Patent 3,714,141, issued in 1973; U.S. Patent 4,568,741 issued in 1986; U.S. Patent 4,710,565, issued in 1984; (all of the foregoing patents being incorporated herein by reference).

Additional knowledge in the art concerning clindamycin is found in Magerlein, et al, Antimicro. Ag. Chemother. (1966) 727; Birkenmeyer and Kagan, J. Med. Chem., 13, 616 (1970); Oesterling, J. Pharm Sci. 59, 63 (1970); McGehee, et al, Am. J. Med. Sci. 256, 279 (1968); D.A. Leigh, J. Antimicrob. Chemother. 7 (Supplement A), 3 (1981); JE Gray et al. Toxicol. Appl. Pharmacol. 21, 516 (1972) and LW Brown and WF Beyer in Analytical Profiles of Drug Substances, Vol 10, K. Florey, editor (Academic Press, New York, 1981) pages 75-91.

Another of the lincosamides, lincomycin, is also known as (2S-trans)-methyl 6,8-dideoxy-6- [[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-D-erythro α-D-galacto-octopyranoside. As used herein the term "lincomycin" alone includes free-base and crystalline free-base forms of lincomycin as well as the pharmaceutically acceptable salts and esters thereof. Examples of pharmaceutically acceptable salts and esters of lincomycin are lincomycin hydrochloride, lincomycin phosphate, lincomycin palmitate and lincomycin palmitate hydrochloride. It is preferred to use a lincomycin salt or ester in the composition of the invention, with lincomycin phosphate being especially preferred.

Lincomycin, its characteristics, and methods of synthesis thereof are set forth in many references, including but not limited to, U.S. Patent No. 3,086,912, in U.S. Patent No. 3,676,302 by Jeronimo Visser, incorporated herein by reference. Methods of synthesis of and descriptions of lincomycin derivative antibiotics suitable for use in the compositions of the present invention are set forth in many references, including, but not limited to, U.S. Patent No. 3,329,568 by Alexander Argoudelis, in U.S. Patent No. 3,359,164 by Alexander Argoudelis, in U.S. Patent No. 3,361,738 by Alexander Argoudelis, in U.S. Patent No. 3,395,139 by Donald Mason.

Another of the lincosamides, pirlimycin, is also known as (2S-cis)-methyl 7-chloro-6,7,8-trideoxy-6-[[(4-ethyl-2-piperidinyl)carbonyl]amino]-1-thio-L-threo-α-D-

galactooctopyranoside. As used herein the term "pirlimycin", alone, includes free-base and crystalline free-base forms of clindamycin as well as the pharmaceutically acceptable salts and esters thereof. Examples of pharmaceutically acceptable salts and esters of pirlimycin are pirlimycin hydrochloride, pirlimycin phosphate, pirlimycin palmitate and pirlimycin palmitate hydrochloride. It is preferred to use a pirlimycin salt or ester in the composition of the invention, with pirlimycin phosphate being especially preferred.

All three preferred types of lincosamides described above, i.e. clincamycin, lincomycin, and pirlimycin, have been administered to various types of animals, as antibiotics. All three have also been used as growth enhancers for meat producing animals. See, for example studies discussed in WO 88/09130.

The lincosamide is preferably present as a solid, in particulate form. The size of the particles depends upon the solubility of the particular lincosamide used, with smaller particles needed for less soluble forms of lincosamides. The volume mean diameter of the solid particles of lincosamides are preferably at least about 0.5 μm to about 500 μm, more preferably 0.5 μm to about 300 μm, even more preferably 0.5 μm to about 150 μm. The particles of the lincosamide are preferably dispersed in a pharmaceutically acceptable carrier, in which the lincosamide is poorly soluble, wherein the composition is adapted for rectal administration. The pharmaceutically acceptable carrier preferably comprises a Hard Fat.

The composition of the present invention must be solid at room temperature, and preferably have a flow point from about 30°C to about 40 °C, more preferably have a flow point from about 30°C to about 37 °C. The flow point is visually determined based upon heating a sample from 25 °C at a rate of 2 °C/minute and observing the temperature at which rapid flow of the sample occurs. This measurement is conveniently carried out using a microscope equipped with a video camera having on-screen digital monitoring of the temperature.

Hard Fat suppository bases undergo a polymorphic transition during storage. The stages of the transition are designated α, α′ and ß, with the ß form being the final, most stable polymorph. Thus, the flow point of a composition immediately after manufacture will increase slowly until the transition is complete. Using conventional

x-ray diffraction techniques, the polymorphic transition from the α to ß forms may be monitored from the time of the initial suppository manufacture until no further changes in the diffraction pattern over a period of time are evident. An example of the α, α′ and ß x-ray diffraction patterns is shown in Figure 1. The flow points described above refer to the flow point following completion of the polymorphic transition.

The composition of the present invention contains an antimicrobially effective amount of lincosamide for the treatment of an antibiotic infection in a subject. The amount of lincosamide appropriate for any given subject depends upon the species of the subject, the weight of the subject, and the dosage equivalency of the particular lincosamide to be administered to the subject. When the lincosamide is clindamycin and the subject is a human adult, the suppository preferably contains about 10 mg to about 800 mg of clindamycin, or a form of clindamycin expressed as the free base, more preferably about 25 mg to about 300 mg, even more preferably about 50 mg to about 200 mg, and most preferably about 50 mg to about 150 mg. Appropriate dosage ranges for other lincosamides, such as lincomycin and pirlimycin can be determined using standard dosage assay techniques, or where the dosage is known, by reference to publications where such known dosage ramges are given.

The total weight of a composition of the invention will vary according to the amount of active ingredient and "ease of use" characteristics such as size and shape of the resulting suppository, and is therefore not critical. Total weight also varies according to the type of subject to which the suppository is to be administered (e.g. cat, dog, horse, or human). Generally, lower amounts of active ingredient may be accommodated by a smaller size suppository, and higher amounts of active ingredient will require a larger size suppository.

Manufacturing properties, such as the viscosity of a lincosamide base dispersion when the base is in the molten state during processing, will also determine the minimum amount of suppository base that is needed to disperse, mold and package a suppository having a given amount of the lincosamide. Such a parameter is not critical to the present invention, and may be determined in the course of routine optimization of the manufacturing process.

The total weight of typical rectal suppositories for human subjects preferably range in size from about 0.5 g to about 10 g, preferably from about 1 g to about 5 g, and most preferably from about 2 g to about 3 g. Human rectal clindamycin suppository compositions would generally be in the range of 0.1% to 60% by weight of clindamycin, preferably 0.5% to 30%, more preferably 1.5% to 10%, and most preferably 1.5% to 7.5% of clindamycin. The percent by weight of lincosamide in the most preferred suppositories of the present invention depends upon the total weight of the suppository and the and the dose required for systemic treatment of an infection of a harmful gram-positive bacteria in subject(s) to be treated therewith.

The suppository bases useful in accordance with the present invention are any pharmaceutically acceptable Hard Fat bases. Hard Fat NF suppository bases useful in the compositions of the present invention are manufactured by Condea Vista Company, Cranford, New Jersey under the WITEPSOL® trademark, and by Stepan Company, Northfield, Illinois under the WECOBEE® trademark. Further useful Hard Fat NF suppository bases are those manufactured by Gattefosse Etablissements, Saint Priest, France under the SUPPOCIRE® trademark. The WITEPSOLs are described by their manufacturer as being "glyceride esters of saturated C_{12}-C_{18} fatty acids." The WECOBEEs are described by their manufacturer as being "a triglyceride derived from vegetable oil." The SUPPOCIREs are described by the manufacturer as hydrogenated palm kernel glycerides and hydrogenated palm glycerides.

Particularly preferred Hard Fat NF suppository bases are a mixture of glyceride esters of vegetable C_{12}-C_{18} saturated fatty acids. The majority of the glyceride esters are preferably triglycerides. The vegetable source is preferably coconut and palm kernel oils. The most preferred Hard Fat NF base for use in the compositions of the present invention is a mixture of triglyceride esters of coconut and palm kernel oil C_{12}-C_{18} saturated fatty acids having the following characteristics in the absence of a lincosamide:

Open-tube melting point:	31.0-33.0 °C (α polymorphic form)
Solidification point:	30.0-32.5 °C (α polymorphic form)
Hydroxyl value	max. 3 mg potassium hydroxide/g
Saponification value:	240-250 mg potassium hydroxide/g
Diglycerides	max. 15% by weight
Monoglycerides	max 1% by weight

All the above tests reported in the specification are performed in accordance with standardized procedures, e.g., United States Pharamacopoeia or European Pharamacopoeia. A commercially available Hard Fat NF base that is described by the vendor as having all of the most preferred properties cited immediately above is WITEPSOL® H-32 (Condea Vista Company, Cranford, New Jersey). A typical composition of a clindamycin suppository of the present invention using WITEPSOL® H-32 is presented in Table 1.

Table 1. Composition of Clindamycin Phosphate Suppository

Amount per Suppository	Component
100 mg [1]	Clindamycin phosphate USP (milled)
2375 mg	Witepsol H-32 (Hard Fat NF)

[1] expressed in terms of the clindamycin free base. Actual amount of clindamycin phosphate used is calculated on the basis of potency assay (e.g., USP).

See Examples 4, 6, 8, and 10, herein below, for illustrations of lincosamide suppositories made with a single dose of each of four different lincosamides.

The Hard Fat base used in the composition and method of the present invention may be produced by any conventional means. One means for producing the Hard Fat base is by blending C_{12}-C_{18} saturated fatty acids, preferably derived from coconut and palm kernel oils, followed by esterifying the mixture with glycerol. Routine variations

in the blend of saturated fatty acids and in the esterification conditions enable the production suppository bases having the desired properties described above.

Hard Fat suppository bases provide a high level of storage stability to clindamycin. Assays carried out after as much as sixty months of storage at room temperature show that virtually no clindamycin degradation has occurred in the suppositories of the invention.

The suppositories of the present invention may also contain additives, such as stabilizers (e.g., antioxidants and other types of preservatives), polymorphic transition accelerators (e.g., tristearin), biocompatible polymers, surfactants, dispersants, water absorbents and the like. The use of biocompatible polymers, surfactants and water absorbents are described in U.S. Patent No. 4,765,978, the disclosure of which is hereby incorporated by reference. The concentration of these additives may vary according to the particular additive used and the desired result sought. The use of the kind and concentration of additives are well within the ability of the skilled artisan.

The lincosamide used in the suppository compositions of the present invention can be present in an unmilled state, particularly when the lincosamide is highly soluble in the environment of the rectum of a subject to which it is to be delivered. However, when the lincosamide is less soluble, the lincosamide is preferably present in the form of particles having a smaller volume mean diameter ("particle size") than unmilled particles. The lincosamide particles preferably are of a particle size that is not so large as to cause rectal irritation in a subject administered the composition of the present invention. When the lincosamide is clindamycin, the clindamycin particles preferably have a particle size of not more than about 10 μm.

The minimum particle size is not critical; but, are preferably not be so small as to cause problems in the manufacture of the suppositories. Lincosamide particle sizes as low as 0.5 μm are suitable for use in the compositions of the present invention.

If the particle size of a bulk sample of a lincosamide is greater than 10 μM, it may be reduced in particle size by any conventional means. However, it is preferably milled using a pulverizing rotary mill or air jet micronizer. With the exception of particle size, the physical and chemical characteristics of the milled drug are preferably the same as the unmilled drug.

A particularly preferred embodiment of the invention is a suppository comprising a lincosamide having a particle size of 10 μM or less dispersed in a Hard Fat NF suppository base. The suppository is solid at room temperature, and has a flow point of 37 °C or less after reaching the ß polymorphic form. In the more preferred embodiment, the Hard Fat NF is a mixture of glyceride esters of vegetable C_{12}-C_{18} saturated fatty acids, the majority of which are triglycerides. In the most preferred embodiment, the Hard Fat NF meets the specifications described previously above.

The suppositories of the present invention may be prepared by any conventional means, such as by hand casting or through the use of an automated "form-fill-seal" suppository machine. In general terms, suppository manufacture may be performed by melting the base to an appropriate selected temperature, incorporating the drug while mixing, and mixing to uniformity. If desired, the molten base may be filtered prior to drug addition, and the drug/base mixture may be homogenized prior to filling. The molten dispersion is maintained at the above selected temperature for filling. If hand filled, the molten base is volumetrically filled into casting molds and allowed to solidify at room temperature. The finished suppositories may then be individually packaged into preformed foil pouches or wrapped. Alternatively, the suppository manufacture may be automated using a form-fill-seal machine. By this method, an open foil shell is formed by the machine and the molten suppository base is volumetrically filled into the shell. The foil is then sealed and the filled shell is transferred to a cooling table or other similar device for solidification. A schematic for preparation of suppositories of the present invention is shown in Figure 2.

The suppository of the present invention is preferably of a size and shape suitable for administration to a subject of interest, such as a subject having a bacterial infection the lincosamide in the suppository is known to treat. In the case of a human being, the suppository is small enough to be inserted through the anus into the rectum, preferably without causing discomfort to the subject. In the case of non-human subjects, the suppository is small enough to be inserted into the rectum through the corresponding opening from the lower digestive tract, collectively referred to as an "anus", herein.

The suppository of the present invention, having characteristics as described above, is preferably administered to a subject by inserting the suppository into the rectum of the subject, through the anus. When the subject is infected with at least one bacteria that is harmful to the subject, the suppository preferably contains a dose of lincosamide sufficient to treat the bacterial infection. Subsequent doses of the lincosamide are preferably administered, in the same way as described above, until all or substantially all traces of the bacterial infection have been removed.

The following examples are illustrative of suppository compositions, methods of making suppositories, and methods of using suppositories of the present invention. They are not to be construed as limiting. All experiments were or are done at room temperature and pressure, unless otherwise indicated.

EXAMPLES

EXAMPLE 1 Preparation of Suppositories of Clindamycin

A batch of 11,200 suppositories was produced using the following procedure:

1. 29 kg of WITEPSOL H-32 Hard Fat NF base was melted in a manufacturing kettle by heating to 40±2°C. The temperature of the molten suppository base was maintained at 40±2°C throughout this manufacturing procedure.
2. Using a preheated filter, 26.614 kg of the molten base was transferred to a second manufacturing vessel equipped with a homogenizing mixer.
3. 1.386 kg of clindamycin phosphate equivalent to 1.12 kg of clindamycin free base was added to the kettle and mixed and homogenized to obtain a uniform dispersion.
4. The drug dispersion was transferred to a jacketed kettle and transported to the form/fill/seal suppository machine.
5. While maintaining mixing and a temperature of 40±2°C, the drug dispersion was formed into 2.5 g suppositories using the automated form/fill/seal machine.

EXAMPLE 2 X-ray Diffraction Examination of Clindamycin Suppositories

The polymorphic transition state of the suppository was determined using a Siemans D-5000 x-ray diffractometer. A sufficient amount of material to fill the diffractometer sample tray was scraped from the suppository and then carefully

packed into the tray to ensure a flat surface. The instrument was operated with copper K-L_3 radiation at a wavelength of 1.5406 Å with a nickel filter. The instrument parameters were as follows: 45KV voltage, 40mA current, 0.2mm detector aperture. The sample was scanned over the spectral range of 3-40° 2θ at a scan rate of 2° 2θ/min. Figure 1 shows typical diffraction patterns as the sample goes through the phase transitions from α to α′ to ß polymorphs.

EXAMPLE 3 Flow Point Determination of Clindamycin Suppository

The flow point of each of several clindamycin suppositories produced as described in Example 1, was determined in the following manner:

A polarizing microscope with a 20 x pol long working distance objective was used in conjunction with a Mettler FP 82 hot stage. A razor blade was used to obtain a small portion of the suppository which was placed on a pre-cleaned slide and covered with a cover slip. Gentle pressure was applied to the cover slip to cause the sample to spread to uniformity, and the slide was placed in the furnace of the hot stage. The sample was heated over the range of 25-40°C at a rate of 2°C/minute. A video camera was used to observe the heating which was recorded with simultaneous on-screen digital display of the temperature. The flow point was defined as the temperature at which rapid flow of the sample occurred.

The flow point of clindamycin suppositories tested one day after manufacture was determined to be 33.3°C. The clindamycin suppositories were stored at 25°C/60% relative humidity prior to testing. The flow point of clindamycin suppositories at 3 months after manufacture was found to be 33.9 °C. At 6 months after manufacture, the flow point of the clindamycin suppositories remained 33.9 °C, demonstrating the excellent stability of the suppository composition.

EXAMPLE 4 Lincomycin Hydrochloride Suppository Preparation

A batch of 80 lincomycin hydrochloride suppositories, each of which was configured to deliver a single dose of lincomycin for treatment of an adult human was produced using the following procedure:

1. 160.0 g of WITEPSOL H-32 Hard Fat NF base was melted in a manufacturing kettle by heating to 40+2°C. The temperature of the molten suppository base was maintained at 40+2°C throughout the manufacturing procedure.

2. 40.0 g of lincomycin hydrochloride was added to the kettle and mixed and homogenized to obtain a uniform dispersion.

3. Each cavity of the suppository mold was filled with 2.5 g of the drug dispersion.

4. The suppository base was cooled over night at room temperature. The following day, the hardened suppositories were removed from the mold.

EXAMPLE 5 Flow Point Determination of Lincomycin Hydrochloride Suppository

The flow point of a lincomycin hydrochloride suppository produced as described in Example 4, above, was determined according to the same procedure described in Example 3, above. The flow point of the lincomycin suppository was determined to be 31.1°C.

EXAMPLE 6 Clindamycin Suppository Preparation

A batch of 120 clindamycin suppositories, each of which was configured to deliver a single dose of lincomycin for treatment of an adult human, was produced using the following procedure:

1. 264.00 g of WITEPSOL H-32 Hard Fat NF base was melted in a manufacturing kettle by heating to 40+2°C. The temperature of the molten suppository base was maintained at 40+2°C throughout the manufacturing procedure.

2. 36.0 g of clindamycin was added to the kettle and mixed and homogenized to obtain a uniform dispersion.

3. Each cavity of the suppository mold was filled with 2.5 g of the drug dispersion.

4. The suppository base was cooled over night at room temperature. The next morning the hardened suppositories were removed from the mold.

EXAMPLE 7 Flow Point Determination of Clindamycin Suppository

The flow point of a clindamycin suppository produced as described in Example 6, above, was determined according to the same procedure described in Example 3, above. The flow point of the clindamycin suppository was determined to be 31.7°C.

EXAMPLE 8 Lincomycin Hydrochloride Suppository Preparation

A batch of 278 lincomycin hydrochloride suppositories was produced using the following procedure:

1. 130.50 g of WITEPSOL H-32 Hard Fat NF base was melted in a manufacturing kettle by heating to 40+2°C. The temperature of the molten suppository base was maintained at 40+2°C throughout the manufacturing procedure.

2. 69.5 g of lincomycin hydrochloride was added to the kettle and mixed and homogenized to obtain a uniform dispersion.

3. Each cavity of the suppository mold was filled with 0.720 g of the drug dispersion.

4. The suppository base was cooled over night at room temperature. The next morning the hardened suppositories were removed from the mold.

EXAMPLE 9 Flow Point Determination of Lincomycin Hydrochloride Suppository

The flow point of a lincomycin hydrochloride suppository produced as described in Example 8, above, was determined according to the same procedure described in Example 3, above. The flow point of the lincomycin hydrochloride suppository was determined to be 31.2°C.

EXAMPLE 10 Pirlimycin Hydrochloride Suppository Preparation

Prepare a batch of 80 pirlimycin hydrochloride suppositories using the following procedure:

1. Melt 192 g of WITEPSOL H-32 Hard Fat NF base in a manufacturing kettle by heating to 40+2°C. Maintain the temperature of the molten suppository base at 40+2°C throughout the manufacturing procedure.

2. Add 8.0 g of milled or micronized pirlimycin hydrochloride to the kettle and mix and homogenize to obtain a uniform dispersion.

3. Fill each cavity of the suppository mold with 2.5 g of the drug dispersion.

4. Cool the suppository base over night at room temperature. The next morning remove the hardened suppositories from the mold.

EXAMPLE 11Effectiveness of Suppository for Treating Bacterial Infection

A prospective, randomized, double-blind, multicenter study is performed to test the effectiveness of any one of the types of single dose suppositories produced as described in Examples 4, 6, 8, or 10, above. Effectiveness of any one of the types of suppositories is studied after three and seven days of rectal administration of the type of suppository over a period of time to adult human subjects infected with at least one gram-positive bacteria, and cure rates after each period of treatment measured. Cure rates are compared to a control group administered placebo suppositories containing no antibiotic. Subjects in the control group undergo a cure rate of at least 80% higher than the control group.